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Title: Polymorphisms of genes involved in extracellular matrix remodeling, xenobiotic metabolism, antioxidant pathways and chronic lung disease in children

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Body: We performed a candidate gene association study of 43 polymorphisms in genes coding genes functioning in extracellular matrix remodeling, xenobiotic metabolism and antioxidant pathways in 257 children with severe chronic lung disease (CLD) and 335 controls. The frequencies of wild type/ wild type genotype of CYP2F1 (c.14_15insC) gene were significantly higher in CLD patients than in the healthy control group (Padj=0.000001; OR=3.16 2.10-4.77). Association with CLD and CYP1A1 gene polymorphisms (3798T>C and 2454A>G) in additive model (Padj=0.0003; OR=1.72 1.28-2.33 and Padj=0.001; OR=2.31 1.28-2.33) was found. The patients with CLD showed significantly elevated frequencies of the GSTT1 gene deletion (Padj=0.0003; OR=1.98 95% CI 1.36-2.89). The GSTP1 (313A>G) polymorphism was associated with CLD (for AA genotype Padj = 0.0046, OR=1.65 1.17-2.34). Regression analysis showed that CAT (-262C>T) CC genotype is associated with a 1.84 -fold increase (95% CI 1.22-2.65; Padj=0.0009) and NQO1 (465C>T) is associated with a 1.89 -fold increase (95% CI 1.19-3.02; Padj=0.006) in additive model. Association with CLD and MMP3 (-1171 5A>6A), MMP12 (-82A>G), MMP9 (2660A>G) and TIMP3 (-1296T>C) gene polymorphisms in dominant model was found (Padj=0.0013, OR=2.75 1.43-5.31; Padj=0.007, OR=1.83 1.16-2.89; Padj=0.017, OR=1.54 1.08-2.21; Padj=0.033, OR=1.48 1.11-2.01) Consequently, CYP2F1, CYP1A1, CAT, GSTP1, GSTT1, NQO1, MMP3, MMP9, MMP12 and TIMP3 genetic polymorphisms probably play a substantial part in susceptibility to severe pulmonary inflammation in children with CLD.